REMARKS

Claims 1, 4-9, 12-15 and 23 are pending in this application. Claims 6-9 and 15 stand withdrawn from further consideration as being drawn to nonelected inventions under 37 C.F.R. § 1.142(b).

Applicant has amended claim 1 to specify that the anti-TWEAK monoclonal antibodies useful in the methods of this invention are monoclonal antibodies that bind specifically to a TWEAK ligand of SEQ ID NO:2. Support for this amendment is found, *e.g.*, at page 5, lines 13-16 and lines 23-25; page 9, lines 6-10 and lines 23-25; page 11, lines 25-30; page 12, line 25-page 13, line 32; page 17, lines 9-12; Example 2 on page 19; and Figure 4 of the specification.

Applicant has amended claim 4 to create antecedent basis for the term "mammal" in claim 5, which depends therefrom. This amendment is supported in the specification at page 7, lines 23-24.

Applicant has amended claim 23 to reflect the amendment to claim 1 regarding the anti-TWEAK monoclonal antibodies useful in the methods of this invention.

The amendments presented herein do not constitute new matter. In sum, claims 1, 4-9, 12-15 and 23 are pending.

THE OBJECTIONS

The Examiner acknowledges applicant's claim to priority under 35 U.S.C. § 365(b) and requests certified copies of the priority documents in this National Stage application from the International Bureau. Applicant stands ready to file those certified copies upon allowance of the pending claims.

THE REJECTIONS

ENABLEMENT

Claims 1, 4-5, 12-14 and 23 stand rejected under 35 U.S.C. § 112, first paragraph, for purportedly lacking enablement. The Examiner acknowledges that the specification is enabling for a method of blocking the development or treating or reducing the severity or effects in a subject having chronic Graft-versus-Host disease comprising administering an anti-TWEAK ligand of SEQ ID NO: 2 monoclonal antibody, wherein said Graft-

versus-Host disease is caused by a combination of a Th1 and a Th2 cell-mediated immune response. However, the Examiner contends that the specification is not enabled for:

(1) a method for blocking the development or treating or reducing the severity or effects of any GVHD in an animal comprising the step of administering any pharmaceutical composition which comprises a therapeutically effective amount of an anti-TWEAK polypeptide monoclonal antibody and a pharmaceutically acceptable carrier, wherein said GVHD is caused by a combination of a Th1 or a Th2 cell-mediated immune response alone in claims 1 and 12-13; and

(2) a method for blocking the development or treating or reducing the severity or effects of any organ transplant failure resulting from graft rejection in an animal comprising the step of administering any pharmaceutical composition which comprises an effective amount of an anti-TWEAK monoclonal antibody and a pharmaceutically acceptable carrier, wherein said immune response is a Th1 cell-mediated immune response in claim 12 or a Th2 cell-mediated immune response in claim 13 or both a Th1 and a Th2 cell-mediated immune response in claim 14.

More particularly, the Examiner asserts that the specification does not enable blocking or treatment of any GVHD caused by a Th1 cell-mediated immune response or by a Th2 cell-mediated immune response, specifically, the more severe lethal acute GVHD syndrome. The Examiner also contends that the specification does not enable blocking the development or treatment of organ transplant failure resulting from graft rejection. In the Examiner's view, GVHD and organ transplant failure are separate conditions and one of skill in the art would not be able to predict the efficacy of anti-TWEAK monoclonal antibody therapy on human organ transplants based on the mouse studies of GVHD. Applicant traverses, based on the following remarks.

The development of both GVHD and organ transplant failure resulting from graft rejection involves a common underlying molecular mechanism and the diseases share similar pathologies. Specifically, in both diseases, T cells must recognize and respond to non-self antigens, and once activated, the T cells differentiate into effector T cells capable of mounting an immune response. T cell activation is an initiating event in a complex cascade of events that commonly underlies T-

cell-dependent immune responses. Interaction of activated T cells with accessory and antigen presenting cells, including B cells, monocytes and macrophages, NK cells, NK-T cells, dendritic cells, and tissues resident cells such as resident fibroblasts, all contribute to the orchestration of the immune response which initially occurs upon antigen presentation within lymphoid organs. As such, the integrity and organization of these cells within lymphoid organs are critical to support effective T cell-dependent immune responses. Similar complexity underlies the function of thus activated T cells, B cells, and accessory cells once these have exited the lymphoid organs and are circulating in the periphery, such that appropriate interaction with peripheral tissues and cells resident in those tissues is achieved to allow the activated cells of the immune system to implement their acquired effector functions. Examples include the trafficking of lymphoid cells such as T cells, B cells, and macrophages, and polymorphonuclear cells resulting in inflamed tissue, or the trafficking of plasma B cells into the bone marrow. The entire system of the orchestrated immune response is regulated by the induction or other regulation of an array of effector proteins and other molecules produced by or expressed upon lymphocytes,

accessory cells, tissue resident cells, or cells such as endothelium and epithelium that line tissue, blood vessel, and lumenal space. Examples of proteins and other molecules underlying the orchestrated immune response are those responsible for immune cell survival and activation, differentiation and effector function, including pro-inflammatory cytokines such as the interferons, the interleukins (*e.g.*, Il-6, Il-8), TNF, effector molecules such as NO and MPO, lymphoid organ chemokines and cytokines, and others. Proteins involved in the trafficking of immune cells, such that inflammatory responses will be supported in the periphery, include pro-inflammatory cytokines, such as TNF, the interferons and the interleukins, and the inflammatory chemokines, such as MCP-1, RANTES, and IP-10, and adhesion molecules including the selectins and integrins, such as VCAM-1 and ICAM-1.

The specification describes that GVHD develops following bone marrow transplants in which the donor's immune cells in the transplanted marrow make antibodies against the host's (patient's) tissues and attack vital organs (*see*, specification page 1, lines 18-19). The specification further discloses that organ transplant failure is a consequence of the

transplant recipient's (host's) immune response to antigens derived from the transplanted organ (*see*, specification page 1, lines 19-20). Therefore, reagents, such as anti-TWEAK antibodies, that are capable of modulating the interactions underlying the development of both diseases at a molecular level, such as T cell activation or, once activated, subsequent immune response events, such as those involving accessory cells or B cells, or the production of or response to lymphoid or pro-inflammatory cytokines, chemokines, or adhesion molecules, or effect T cell differentiation, or the subsequent trafficking or effector function of T cells and lymphoid cells, are useful to the development or prevention of consequent pathological conditions. It is this ability to influence the development of the immune response precedent to GVHD and organ transplant failure at a molecular level that is key to the efficacy of anti-TWEAK antibodies in the methods of this invention. Accordingly, the Examiner's focus on the subsequent pathology of GVHD -- whether or not the immune response is Th1 or Th2 cell-mediated and whether or not it is acute or chronic -- is totally misplaced. Based on such capability, one of skill in the art would appreciate that the methods of this invention are useful

for blocking, treating or reducing the severity of either GVHD or organ transplant failure by using a monoclonal antibody that binds to a TWEAK ligand characterized by SEQ ID NO:2, as provided by the specification.

Nevertheless, applicant believes that the Examiner's acknowledged enablement of methods of blocking the development or treating or reducing the severity or effects in a subject having chronic GVHD carries over to methods for treating acute GVHD caused by a Th1 or a Th2 cell-mediated immune response. As discussed above, GVHD, either the acute or the chronic form, develops from a common molecular etiology. Due to this commonality and given the activity of anti-TWEAK monoclonal antibodies in the animal studies included in the specification, one of skill in the art would appreciate that anti-TWEAK monoclonal antibodies would be effective in blocking or treating acute GVHD caused by a Th1 or a Th2 cell-mediated immune response.

As cited on page 4, lines 17-18 of the specification, *Krenger and Ferrara* provides evidence that acute GVHD is a Th1 mediated disease. *See*, Krenger and Ferrara, *Immunol. Res.* 15:50-

73 (1996), attached as Exhibit C with the amendment filed February 27, 2003. *Krenger and Ferrara* discusses the emerging importance of cytokine balance and in particular, of cytokines produced by CD4+ Th1 and CD4+ Th2 cells, in governing the development of GVHD following allogenic bone marrow transplantation. In particular, *Krenger and Ferrara* describes the development of acute GVHD as a three-step process associated with the preferential activation of donor T cells secreting IL-2 and IFN-γ. *Krenger and Ferrara* also discusses that the less severe chronic form of GVHD is characterized as a type 2 cytokine response where IL-4 and IL-10 are preferentially produced. *Id.* at page 61, column 2, lines 29-33 and 38-43, page 62, column 1, lines 2-10. As cited on page 4, lines 17-18 of the specification, *Williamson et al.* also provides evidence that IL-12, a pivotal cytokine in polarizing Th1 cell-mediated immune responses, plays an important role in the development of acute GVHD. *See*, Williamson et al., *J. Immunol.* 157:689-699 (1996), attached hereto as Exhibit 1. As cited on page 4, lines 33-34 of the specification, *De Wit et al.* provides evidence that chronic GVHD appears to be a Th2 T cell-mediated disease. *See*, De Wit et al., *J. Immunol.* 150:361-366 (1993), attached hereto as Exhibit

2. Specifically, *De Wit et al.* discusses that chronic GVHD is characterized by a selective deficiency in cells secreting IL-2 and IFN-γ and a hyperactivation of Th2 cells, with elevated IL-4 production. All of the above references demonstrate that one factor influencing the development of either acute or chronic GVHD involves the development of an immune response to foreign non-self antigens and a critical balance between the cytokines generated by CD4+ Th1 and Th2 cells.

The specification illustrates that the acute form of GVHD occurs within the first two months following bone marrow transplant, whereas the chronic form of the disease is manifested much later (over 100 days post-BMT) (*see*, specification page 5, lines 7-11). The development of acute GVHD also is predictive of the subsequent development of chronic GVHD, such that the same patient may develop both diseases in sequence (see, specification page 3, lines 34-38 and page 4, line 1). Thus, although the different forms of GVHD are characterized by the timing of the onset of the condition, both the acute and chronic forms of GVHD stem from a similar pathological origin, *i.e.*, where the immunocompetent cells from a graft attack the cells and organs of an immunocompromised host. Accordingly, based on the teachings

in the instant specification and the understanding in the art at the time, one of skill in the art would be able to practice the method of treating acute GVHD caused by an immune response to foreign non-self antigen, and the subsequent development of a Th1 or a Th2 cell-mediated pathology using the same monoclonal antibody that binds to a TWEAK ligand characterized by SEQ ID NO:2 without undue experimentation.

Furthermore, the animal studies described in the specification involve models for GVHD well-established in the art at applicant's effective filing date (January 14, 2000). The specification states on page 4, line 4, that GVHD can be modeled in the mouse by transferring parental cells into an F1 host. As previously discussed, GVHD involves the donor's immune cells in the transplanted marrow making antibodies against the host's tissues and attacking vital organs. Organ transplant failure is a consequence of the activation of the transplant recipient's (host's) immune response to antigens derived from the transplanted organ. However, both conditions involve introducing a graft into a host or recipient with the subsequent activation of the immune system. Given the similarities between the pathophysiology between GVHD and organ transplant failure, one of

skill in the art would immediately recognize that anti-TWEAK antibodies could be used to treat organ transplant failure resulting from graft rejection, based on the effects of such antibodies demonstrated in the mice studies of GVHD in the specification.

The Examiner also asserts that numerous factors, other than administration of anti-TWEAK monoclonal antibodies, can affect the treatment protocol. Given the understanding in the art as to the pathophysiology of the target diseases, as well as the activity of anti-TWEAK antibodies disclosed in the specification, viewed together with the factors enumerated at page 16, lines 3-5 of the specification for determining a therapeutically effective dosage regimen, applicant respectfully submits that one of skill in the art would be able to carry out the methods of this invention without undue experimentation. Thus, the Examiner's reliance on *Toogood et al.* is misplaced.

For all the foregoing reasons, amended claim 1 and the claims dependent therefrom (i.e., claims 4-5, 12-14 and 23) are enabled.

WRITTEN DESCRIPTION

Claims 1, 4-5, 12-14 and 23 stand rejected under 35 U.S.C. § 112, first paragraph, for purportedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of filing, had possession of the claimed invention. Applicant traverses, based on the foregoing claim amendments and the following remarks.

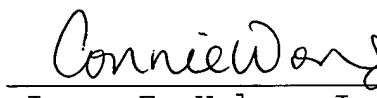
First, applicant submits that amended claim 1 and the claims dependent therefrom (i.e., claims 4-5, 12-14 and 23) satisfy the written description requirement. Applicant has amended claim 1 to specify that the monoclonal antibodies useful in the methods of this invention are those which specifically bind to a TWEAK ligand characterized by the specific amino acid sequence of SEQ ID NO:2. Applicant has also provided sufficient support in the specification that the monoclonal antibody recited in amended claim 1 is useful in blocking or treating GVHD in the murine model of GVHD (*see*, Example 2 of the specification). Furthermore, considering the routine art-recognized field of generating antibodies to fully characterized antigens, one of skill in the art having in hand the TWEAK ligand as defined by

the amino acid sequence of SEQ ID NO:2, would immediately recognize that a spectrum of antibodies that can bind to such a sequence were implicitly disclosed as a result of the disclosure of the TWEAK protein defined by SEQ ID NO:2. Accordingly, applicant has provided sufficient written description to evidence possession of the genus and applicant requests withdrawal of this rejection.

CONCLUSIONS

For the foregoing reasons, applicant believes the claims to be in condition for allowance and respectfully requests that this application be passed to issue.

Respectfully submitted,



James F. Haley, Jr. (Reg. No. 27,794)
Margaret A. Pierri (Reg. No. 30,709)
Attorneys for Applicant
Connie Wong (Limited Recognition)
Agent for Applicant

FISH & NEAVE
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020-1105
Tel.: (212) 596-9000
Fax: (212) 596-9090